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# The Survival Benefits of Antiretroviral Therapy in South Africa

Michael D. April,<sup>1,2,5</sup> Robin Wood,<sup>13,14</sup> Bethany K. Berkowitz,<sup>5</sup> A. David Paltiel,<sup>12</sup> Xavier Anglaret,<sup>15,16,17</sup> Elena Losina,<sup>2,3,8,10</sup> Kenneth A. Freedberg,<sup>2,3,4,5,6,7,9</sup> and Rochelle P. Walensky<sup>2,3,5,6,7,11</sup>

<sup>1</sup>Department of Emergency Medicine, San Antonio Uniformed Services Health Education Consortium, Texas; <sup>2</sup>Harvard Medical School, <sup>3</sup>Center for AIDS Research, and <sup>4</sup>Department of Health Policy and Management, Harvard School of Public Health, Harvard University, <sup>5</sup>The Medical Practice Evaluation Center, <sup>6</sup>Division of Infectious Diseases, and <sup>7</sup>Division of General Medicine, Massachusetts General Hospital, <sup>8</sup>Department of Biostatistics and <sup>9</sup>Department of Epidemiology, Boston University, and <sup>10</sup>Department of Orthopedic Surgery and <sup>11</sup>Division of Infectious Diseases, Brigham and Women's Hospital, Boston, Massachusetts; <sup>12</sup>Yale School of Public Health, New Haven, Connecticut; <sup>13</sup>Desmond Tutu HIV Centre, Institute of Infectious Disease and Molecular Medicine, and <sup>14</sup>Department of Medicine, University of Cape Town, Cape Town, South Africa; <sup>15</sup>INSERM, Centre 897, and <sup>16</sup>Université Bordeaux Segalen, Bordeaux, France; and <sup>17</sup>Programme PAC-CI/ANRS Research Site in Abidjan, Côte d'Ivoire

(See the editorial commentary by Vermund on pages 483–5.)

**Background.** We sought to quantify the survival benefits attributable to antiretroviral therapy (ART) in South Africa since 2004.

**Methods.** We used the Cost-Effectiveness of Preventing AIDS Complications–International model (CEPAC) to simulate 8 cohorts of human immunodeficiency virus (HIV)–infected patients initiating ART each year during 2004–2011. Model inputs included cohort-specific mean CD4<sup>+</sup> T-cell count at ART initiation (112–178 cells/μL), 24-week ART suppressive efficacy (78%), second-line ART availability (2.4% of ART recipients), and cohort-specific 36-month retention rate (55%–71%). CEPAC simulated survival twice for each cohort, once with and once without ART. The sum of the products of per capita survival differences and the total numbers of persons initiating ART for each cohort yielded the total survival benefits.

**Results.** Lifetime per capita survival benefits ranged from 9.3 to 10.2 life-years across the 8 cohorts. Total estimated population lifetime survival benefit for all persons starting ART during 2004–2011 was 21.7 million life-years, of which 2.8 million life-years (12.7%) had been realized by December 2012. By 2030, benefits reached 17.9 million life-years under current policies, 21.7 million life-years with universal second-line ART, 23.3 million life-years with increased linkage to care of eligible untreated patients, and 28.0 million life-years with both linkage to care and universal second-line ART.

**Conclusions.** We found dramatic past and potential future survival benefits attributable to ART, justifying international support of ART rollout in South Africa.

**Keywords.** HIV; South Africa; highly active antiretroviral therapy.

South Africa's human immunodeficiency virus (HIV) epidemic is the largest in the world, with 5.6 million HIV-infected persons in 2011, as estimated by the Joint United Nations Programme on HIV/AIDS (UNAIDS) [1]. Of these, roughly 2.6 million met antiretroviral

therapy (ART) eligibility criteria in 2012. This number in part reflects the expansion of eligibility criteria from a CD4<sup>+</sup> T-cell count of <200 cells/μL or World Health Organization (WHO) stage 4 illness in 2004 [2] to include patients with multidrug-resistant (MDR) tu-

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Correspondence: Michael D. April, MD, DPhil, MSc, Medical Practice Evaluation Center, Massachusetts General Hospital, 50 Stanford St, 9th Fl, Boston, MA 02114 (michael.d.april@post.harvard.edu).

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berculosis or patients with non-MDR tuberculosis and a CD4<sup>+</sup> T-cell count of < 350 cells/ $\mu$ L in 2010 [3]. Yet, despite impressive commitments to expand access to ART [4], one-third (800 000) of these eligible individuals remained without treatment. Meanwhile, current economic challenges have prompted resource-allocation debates that might jeopardize the ongoing treatment of individuals who are already receiving ART and the linkage to care of untreated patients who are eligible for treatment.

We sought to invigorate discussions of prioritizations for HIV care by quantifying both the cumulative survival benefits of ART since its introduction in South Africa in 2004 [5] and the additional returns that could be obtained via expanded rollout investments. Previous studies provide indirect evidence of the survival benefits conferred by ART in sub-Saharan Africa. During 2001–2011, the estimated number of HIV-infected persons living in sub-Saharan Africa steadily increased from 20.9 million to 23.5 million; during this time horizon, owing to the roll out of ART, annual HIV-related deaths decreased by 600 000 (32%) during 2005–2011 [6]. In African countries focused on by the US President's Emergency Plan for AIDS Relief (PEPFAR), national mortality rates [7] were lower during 2004–2008 compared with nonfocus countries [8]. Comparison of adult life expectancy before and after ART rollout in rural KwaZulu Natal revealed an 11.3-year increase [9]. However, to our knowledge, no prior studies have quantified the direct impact of ART rollout on population survival. The objective of our study was to use computer simulation to quantify this impact in South Africa and, by extension, to extrapolate the future survival benefits of further ART rollout.

## METHODS

### Analytic Overview

Survival benefits attributable to ART in South Africa were estimated using the Cost-Effectiveness of Preventing AIDS Complications–International model of HIV disease and treatment (CEPAC) [10–13]. We defined 8 independent cohorts representing adult (age, >14 years) HIV-infected persons initiating ART in a given year during 2004–2011. The size of each cohort was derived from UNAIDS reports [1]. These included only persons who initiated therapy in that year. As the simulation progressed, each of these cohorts experienced attrition through mortality and loss to follow-up. No new patients were added to the cohorts after simulation start.

CEPAC simulated the experience of individual HIV-infected persons; the results of many individual simulations were aggregated to project population-level outcomes. Two simulations were run for each cohort; in one simulation all members initiated ART, and in the other no members initiated ART. Comparison of cohort survival between the ART and no-ART simulations yielded cohort-specific per capita survival benefits

attributable to ART. The initial size of each cohort was calculated using published reports of numbers of persons receiving ART each year [1] and ART program retention ([Supplementary Materials](#)) [14, 15]. Total survival benefits were calculated by adding the products of per capita survival benefits and initial size of each treated cohort. Benefits were distinguished between those already realized (censored as of December 2012) versus those yet to be realized (censored as of December 2030 and uncensored), given conservative assumptions of no new patients initiating ART after 2011 and no improvements in HIV-related care or ART efficacy.

### Model Overview

CEPAC is a state-transition microsimulation model of HIV disease [10–13]. CEPAC simulates each HIV-infected person's lifetime as a series of monthly transitions between health states representing asymptomatic HIV infection, symptomatic HIV infection, and death. Health states are designed to predict disease progression, as reflected by probabilities of transition to other states. Health states are stratified by prognostic indicators, including HIV disease history (eg, past opportunistic disease), CD4<sup>+</sup> T-cell count, and HIV RNA level. HIV RNA level drives the rate of CD4<sup>+</sup> T-cell count decline in the absence of treatment [16]. CD4<sup>+</sup> T-cell count, in turn, determines the monthly probabilities of developing an opportunistic disease or dying. The monthly risk of HIV-related mortality is generally higher for symptomatic states than for asymptomatic states [17]. There is also a monthly age- and sex-stratified risk of non-HIV-related death for all individuals [18].

The efficacy of trimethoprim-sulfamethoxazole prophylaxis (which is assumed available to all patients [19]) is modeled as a reduction in the CD4<sup>+</sup> T-cell count–dependent risk of opportunistic disease (including bacterial diseases, toxoplasmosis, and pneumocystosis). ART efficacy is modeled as a reduction in HIV RNA level with a concomitant increase in CD4<sup>+</sup> T-cell count, as well as a resultant decrease in the probabilities of HIV-related death and all opportunistic diseases. In accordance with WHO guidelines, first-line ART failure is defined as the development of a WHO stage 3 or 4 opportunistic disease or a CD4<sup>+</sup> T-cell count decrease below either the pre-ART nadir, 100 cells/ $\mu$ L absolute value, or 50% of the peak value [20]. Treatment for patients experiencing first-line therapy failure (defined, in the assumed absence of HIV RNA load monitoring, as onset of an opportunistic disease or achievement of CD4<sup>+</sup> T-cell count failure criteria) entailed transition to second-line ART, if available. To reflect treatment resource limitations, the availability of second-line ART for simulated persons in whom first-line therapy failed was limited to the percentage of all ART recipients (2.4%, as reported by the WHO [21]) who were receiving second-line therapy (including those in whom first-line therapy did not fail) in low- and middle-income countries outside of the Americas.

We ran simulations of 1 million patients with and 1 million patients without ART for each cohort to achieve stable per capita survival benefit estimates. Comparison of per capita survival between the simulations with and those without ART yielded cohort-specific per capita survival benefit estimates. The sum of the products of CEPAC-generated per capita survival benefits and numbers of persons initiating ART for each cohort (see cohort size estimates, below) yielded the total number of life-years attributable to ART initiated during 2004–2011 ([Supplementary Materials](#)).

### Model Inputs

We used data from the Southern African Catholic Bishops Conference cohort to estimate mean age  $\pm$  SD ( $37 \pm 10$  years), sex distribution (33% male), HIV RNA level distributions (46% with an HIV RNA level of  $> 100\,000$  copies/mL), and mean CD4<sup>+</sup> T-cell count at ART initiation (112–178 cells/ $\mu$ L during 2004–2011) of the simulated cohorts [22, 23]. HIV disease natural history parameters, including chronic AIDS mortality and opportunistic disease incidence and mortality, were taken from the Cape Town AIDS Cohort [17]. Non-HIV mortality was estimated using United Nations life tables for South Africa, with adjustment to remove HIV-related mortality [18].

Longitudinal cohort analysis yielded the effect of ART (independent of CD4<sup>+</sup> T-cell count rise) on additional reductions in chronic AIDS mortality (56%–96%) and opportunistic disease incidence (32%) [24]. Derived ART efficacy parameters included a 6-month HIV RNA suppression probability of 78% [25], a mean CD4<sup>+</sup> T-cell count increase 6 months after ART initiation of 148 cells/ $\mu$ L [26], and a 0.8% monthly probability of virologic rebound after 6 months for those in whom the HIV RNA level was initially suppressed (Table 1) [25].

### Cohort Size Estimates

We estimated the number of persons initiating ART each year (ie, the initial size of each cohort), using data from the Joint United Nations Programme on HIV/AIDS (UNAIDS) [1]. These data describe the number of persons receiving ART each year but do not specify when they initiated ART. We therefore calculated the difference between the UNAIDS-reported total number of persons receiving ART during December of a given year and the total receiving ART during December of the previous year. This latter number was adjusted downward to reflect attrition due to both loss to follow-up and mortality [14, 15, 27, 28]. In the case of the first cohort, which initiated therapy in 2004, the UNAIDS-reported value was assumed to represent exactly the number of persons initiating ART during that year, because there were no data from earlier reported cohorts to subtract.

Annual cohort attrition comprised losses due to both mortality and loss-to-follow-up as reported by meta-analyses: 18.5%–27.6% during the first year, 8.3%–19.8% during the

**Table 1. Model Parameter Inputs**

Model Parameter	Base-Case Value	Range Examined
<b>Cohort characteristic<sup>a</sup></b>		
Age, y, mean $\pm$ SD [22, 23]	37 $\pm$ 10	. . .
Male sex, subjects, % [22, 23]	33	. . .
CD4 <sup>+</sup> T-cell at ART initiation, cells/ $\mu$ L, mean $\pm$ SD [22, 23]		
2004	112 $\pm$ 95	38–157
2005	127 $\pm$ 124	38–172
2006	133 $\pm$ 133	46–178
2007	145 $\pm$ 143	51–189
2008	149 $\pm$ 132	52–197
2009	156 $\pm$ 147	56–197
2010	178 $\pm$ 345	70–232
2011	173 $\pm$ 144	73–230
Initial HIV RNA level, patients, % [22, 23]		
$> 100\,000$ copies/mL	46	. . .
30 001–100 000 copies/mL	33	. . .
10 001–30 000 copies/mL	21	. . .
$< 10\,001$ copies/mL	0	. . .
<b>Disease natural history</b>		
Monthly risk of AIDS-attributable death without ART, patients, %, by CD4 <sup>+</sup> T-cell count <sup>b</sup> [17]		
0–50 cells/ $\mu$ L	4–10	. . .
51–100 cells/ $\mu$ L	2–5	. . .
101–200 cells/ $\mu$ L	1–3	. . .
201–350 cells/ $\mu$ L <sup>c</sup>	0	. . .
351–500 cells/ $\mu$ L <sup>c</sup>	0	. . .
$> 500$ cells/ $\mu$ L <sup>c</sup>	0	. . .
<b>Antiretroviral therapy</b>		
ART efficacy, 2 lines (NNRTI + 2 NRTIs and PI + 2 recycled NRTIs) <sup>b</sup>		
HIV RNA suppression at 6 mo, patients, % [25]	78	54–97
CD4 <sup>+</sup> T-cell count increase at 6 mo, cells/ $\mu$ L, mean [26]	148	102–225
Monthly risk of ART failure after 6 mo once suppressed, % [25]	0.8	0.4–0.9
Second-line ART availability, all patients receiving ART, % [21]	2.4	0–4.8
ART program retention at 12 mo, patients, % <sup>d</sup> [14, 15, 27, 28]	72.4–81.5	63.8–81.5

Abbreviations: NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; PI, protease inhibitor

<sup>a</sup> Model inputs were derived from additional analysis of the primary dataset on which the cited papers reported.

<sup>b</sup> Ranges reflect distributions of base-case inputs, based on each person's history of opportunistic disease.

<sup>c</sup> Input values are nonzero but are reported as zero because of rounding.

<sup>d</sup> Ranges reflect value differences in retention for each of the 8 cohorts (see Methods).

second year, 5.4%–5.8% during the third year, and 2.6%–2.8% thereafter ([Supplementary Table 1](#)) [14, 15, 27, 28]. These base-case retention loss estimates exceed those reported by various South African cohorts with 5–6 years of follow-up data [29,

**Table 2. Survival Benefits Attributable to Antiretroviral Therapy (ART) in South Africa**

Cohort Year of ART Initiation	A: Persons Initiating ART, No. <sup>a</sup>	Censored at December 2012, Life-Years				Not Censored (Lifetime Benefits), Life-Years			
		B: Per Capita Life Expectancy, Simulation With ART	C: Per Capita Life Expectancy, Simulation Without ART	D: Per Capita Survival Benefit, 2004–2012 <sup>b</sup> [B – C]	E: Survival Benefit, 2004– 2012 [A × D]	B': Per Capita Life Expectancy, Simulation With ART	C': Per Capita Life Expectancy, Simulation Without ART	D': Per Capita Survival Benefit, Lifetime [B' – C']	E': Survival Benefit, Lifetime [A × D']
2004	50 100	5.9	1.9	4.0	199 300	11.2	1.9	9.3	463 800
2005	152 100	5.5	2.1	3.4	518 700	11.5	2.1	9.4	1 429 100
2006	154 700	5.0	2.2	2.8	442 200	11.7	2.2	9.5	1 469 300
2007	182 600	4.4	2.2	2.2	396 900	11.6	2.3	9.3	1 694 300
2008	314 900	3.8	2.2	1.6	522 600	12.1	2.3	9.8	3 082 700
2009	319 000	3.1	2.0	1.1	333 500	12.3	2.4	9.9	3 152 300
2010	491 900	2.3	1.8	0.5	240 400	13.0	3.3	9.7	4 768 900
2011	557 300	1.4	1.2	0.2	99 300	12.7	2.5	10.2	5 671 000
Total	2 222 700				2 752 800				21 731 300

<sup>a</sup> Calculated using reports of numbers of persons receiving ART each year [1] and ART program retention losses [14, 15].

<sup>b</sup> Calculated by subtracting life expectancies during 2004–2012 for the no-ART simulations (column C) from those for the ART simulations (column B). Survival gains in 2004 are thus measured over 9 years, whereas those in 2011 are measured over 2 years.

30]. In subsequent years (2005–2011), the numbers of persons assigned to start in each cohort were calculated such that the number of persons alive across all cohorts summed to UNAIDS-reported numbers of persons receiving ART in South Africa each year [1]. In this way, we ensured that the model cohort sizes never exceeded the numbers of persons reported to be receiving ART by UNAIDS data. After the eighth cohort initiated treatment, in 2011, no additional persons were added to the analysis (Supplementary Materials). Once patients were lost to follow-up, they were assumed to never re-enter care to make our survival gain estimates more conservative.

### Sensitivity Analyses

We conducted sensitivity analyses to examine the impact of uncertainty in base-case parameter input values (Table 1) and assumptions on projected survival benefits. These analyses included alternative inputs reflecting uncertainty in numbers of persons initiating ART each year [1], mean CD4<sup>+</sup> T-cell count upon ART initiation [22, 23], CD4<sup>+</sup> T-cell count and HIV RNA level monitoring availability [20, 31, 32], ART efficacy [26, 33–37], second-line ART availability [21], and ART program retention (Supplementary Materials) [14, 15]. We also simultaneously changed all of these variables to generate best- and worst-case scenarios reflecting uncertainty in all base-case inputs.

### Additional Analyses

Additional analyses examined outcomes through 2030 for scenarios in which prospective policy decisions accelerate the roll out of HIV treatment services as of January 2014. These

scenarios included universal access to second-line ART (rather than the base-case 2.4% availability) and future annual linkage to care of eligible HIV-infected persons not yet receiving ART. The latter scenarios assumed that 34% of eligible patients were not yet receiving ART [1], that the HIV-infected population size grew according to the projections by the Actuarial Society of South Africa [38], and that 10% of untreated eligible patients were linked to care each year. Maximum potential benefits from increased linkage to care were projected by examining alternative annual rates of linkage to care up to 84% [39].

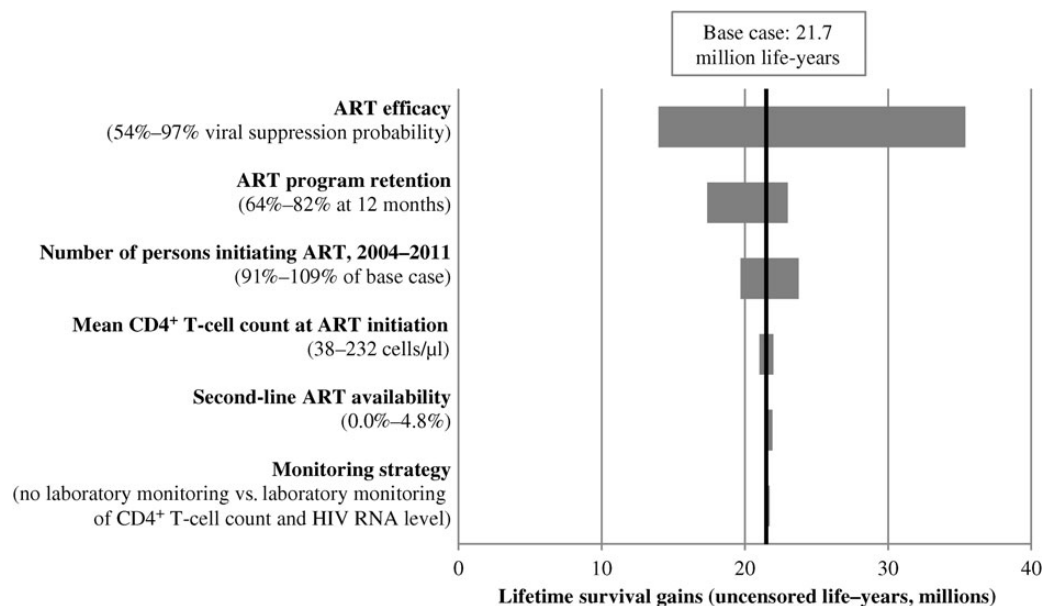
## RESULTS

### Survival Benefits

The number of persons initiating ART each year grew from 50 100 in 2004 to 557 300 in 2011. In total, 2 222 700 individuals were estimated to have initiated ART during 2004–2011. Regarding censored survival benefits, the cohort initiating ART in 2004 had an estimated per capita life expectancy of 1.9 years in the simulation without ART, compared with 5.9 years in the simulation with ART, for a per capita increase of 4.0 life-years. Censored per capita survival benefits decreased for subsequent cohorts, with a low of 0.2 life-years for the cohort initiating ART in 2011. The sum of products of the numbers of patients newly initiating ART and the censored per capita survival benefits yielded an estimated 2.8 million life-years as of December 2012 (Table 2).

Regarding lifetime (uncensored) survival benefits, the cohort initiating ART in 2004 had an estimated per capita life expectancy of 1.9 years in the simulation without ART, compared with 11.2 years in the simulation with ART, for a per capita increase





**Figure 1.** Results of univariate sensitivity analyses. The analyses examined the impact of adjusting selected model parameter values (individual bar labels) on the basis of cumulative survival benefits attributable to antiretroviral therapy (ART) in South Africa, in life-years (horizontal axis). The ranges of input values for each parameter are indicated alongside the corresponding bar graph. Results were most sensitive to ART efficacy, ART program retention, and the numbers of persons initiating ART. Abbreviation: HIV, human immunodeficiency virus.

of 9.3 life-years. Per capita survival benefits for subsequent cohorts were comparable, ranging from 9.3 to 10.2 life-years. The sum of products of the numbers of patients newly initiating ART and the lifetime per capita survival benefits yielded an estimated 21.7 million life-years (Table 2). Of this expected total, 18.9 million life-years (87.3%) had yet to be attained.

### Univariate Sensitivity Analyses

Univariate sensitivity analyses demonstrated that the base-case lifetime survival benefit estimate (21.7 million life-years) was most sensitive to uncertainty regarding ART efficacy (probability of initial viral suppression, CD4<sup>+</sup> T-cell count rise, and probability of late ART failure), yielding lifetime survival benefits ranging from 14.0 to 35.4 million life-years. Lifetime survival benefits were also sensitive to ART program retention (17.4–23.0 million life-years) and numbers of persons receiving ART (19.7–23.7 million life-years). Lifetime survival benefits were comparatively insensitive to the WHO monitoring guidelines followed for guiding the transition to second-line ART, uncertainty in the availability of second-line ART, and CD4<sup>+</sup> T-cell count at ART initiation (Figure 1).

### Best- and Worst-Case Scenarios

All ranges of values used in the univariate analyses were used simultaneously in a multivariable analysis to establish worst- and best-case scenarios reflecting uncertainty in all variables listed in Figure 1. In the worst-case scenario, lifetime survival benefits reached 10.2 million life-years, of which 2.2 million life-years

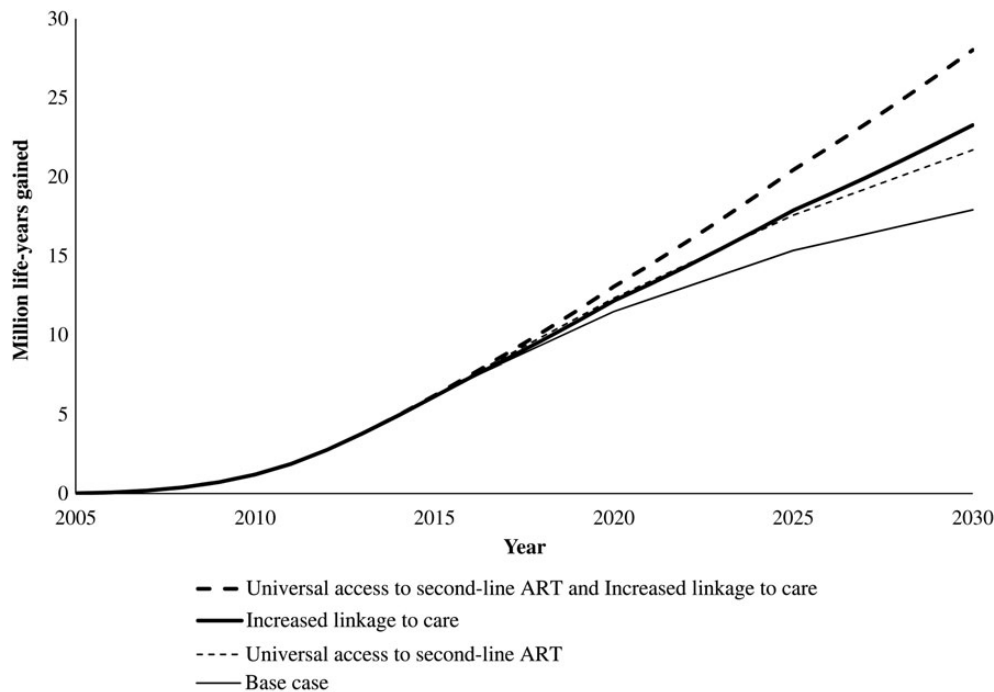
(21.8%) had already been realized as of December 2012. The best-case scenario resulted in lifetime survival benefits of 37.6 million life-years, of which 3.0 million (8.1%) had already been realized.

### Prospective Policy Analyses Projections to 2030

Additional analyses examined hypothetical scenarios of implementing various policy initiatives associated with HIV treatment and linkage to care in January 2014, projected to December 2030 (Figure 2). The base-case survival benefits were projected to reach 17.9 million life-years. A scenario of universal access to second-line ART starting in January 2014 increased these benefits to 21.7 million life-years. Implementation of annual linkage to care of 10% of eligible untreated HIV-infected patients yielded 23.3 million life-years. Finally, universal access to second-line ART coupled with expanded case detection yielded 28.0 million life-years.

### Maximum Potential Benefits

Additional analyses demonstrated the sensitivity of these future projections through December 2030 to the annual proportion of untreated HIV-infected persons assumed to be linked to care each year with expanded testing (Figure 3). Survival benefits plateau with increasing linkage-to-care rates; at higher rates nearly all eligible patients are ultimately linked to care and so additional rate increases do not increase numbers of patients ultimately receiving ART but rather only achieve earlier ART initiation. In a scenario of increased linkage to care only and base-case availability of second-line ART for no more than 2.4%



**Figure 2.** Survival benefits in South Africa following implementation of expanded human immunodeficiency virus (HIV) treatment and linkage-to-care policies, 2004–2030. Projections assume an annual HIV-infected population size projected by the Actuarial Society of South Africa [38]. The projections are depicted as cumulative survival benefits in millions of life-years (vertical axis), as a function of calendar year (horizontal axis). The vertical line demarcates January 2014, the time at which increased linkage to care and treatment is assumed to begin. Base-case survival benefits reached 17.9 million life-years by December 2030 (solid gray line). Universal access to second-line antiretroviral therapy (ART) starting in January 2014 yielded 21.7 million life-years (dashed grey line). Linkage to care of 10% of eligible untreated HIV-infected patients each year yielded 23.3 million life-years by 2030 (solid black line). Finally, universal access to second-line ART coupled with expanded case detection yielded 28.0 million life-years by 2030 (dashed black line).

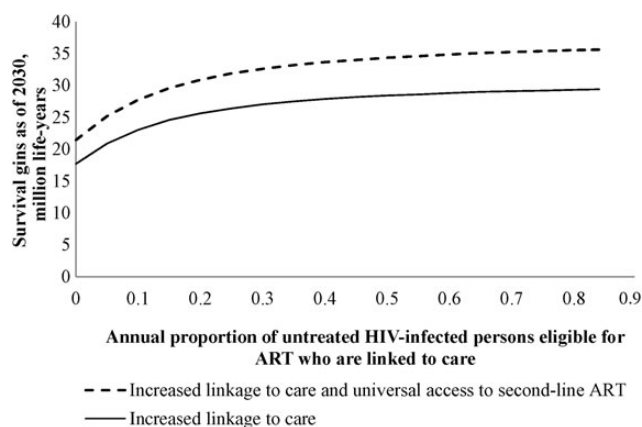
of ART recipients at any given time, survival benefits as of 2030 reached 25.9 million life-years with 20% linkage to care and up to 29.4 million life-years with 84% linkage to care. In a scenario of universal access to second-line ART starting in 2014, survival benefits as of 2030 reached 31.2 million life-years with 20% linkage to care and up to 35.6 million life-years with 84% linkage to care.

## DISCUSSION

We provide a model-based estimate of the survival benefits attributable to ART in South Africa. In the base case, 21.7 million life-years were attributable to ART over the lifetime of all persons initiating ART during 2004–2011, of which only 2.8 million life-years (12.7%) had been realized as of December 2012. Implementation of expanded testing and treatment policies starting in 2014 were projected to significantly increase these benefits. By 2030, survival benefits will reach 17.9 million life-years under current policies, assuming no new patients initiate ART. This is only 82% of the potential benefits with universal second-line ART access (21.7 million life-years), 77% of the benefits with annual linkage to care of 10% of untreated

eligible patients (23.3 million life-years), and 50% of the potential benefits with annual linkage to care of 84% of untreated eligible patients and universal second-line ART access (35.6 million life-years).

This study contributes to a growing literature establishing the profound survival benefits resulting from investments in the global response to the HIV pandemic [8, 40, 41]. Approximately \$13.7 billion was invested in 2008 alone, including 31% from direct bilateral funding (namely PEPFAR), 12% from multilateral institutions (including the Global Fund), and 5% from philanthropic sources, such as the Bill and Melinda Gates Foundation [27, 42]. These investments have already saved millions of life-years, but this analysis highlights that little more than one-tenth of the survival benefits made possible by current policies have been realized in South Africa. Furthermore, these benefits may be substantially increased through more-aggressive linkage to care of untreated eligible HIV-infected patients and expansion of access to second-line ART. Realizing the full potential return on investments already made will require that funding sources remain committed to maintaining and expanding resources available for monitoring, retention, and treatment.



**Figure 3.** Sensitivity analyses of survival benefit projections following expanded human immunodeficiency virus (HIV) treatment and linkage-to-care policies in South Africa. Survival benefits are reported in millions of life-years as of December 2030 (vertical axis). Sensitivity analyses examined alternative values for the annual proportion of untreated HIV-infected persons eligible for antiretroviral therapy (ART) who are linked to care each year as a result of expanded testing (horizontal axis). In a scenario of increased linkage to care only and base-case availability of second-line ART for no more than 2.4% of ART recipients at any given time, survival benefits as of 2030 reached 25.9 million life-years with 20% linkage to care and 29.4 million life-years with 84% linkage to care (solid line). In a scenario of universal access to second-line ART starting in 2014, survival benefits as of 2030 reached 31.2 million life-years with 20% linkage to care and 35.6 million life-years with 84% linkage to care (dashed line).

Our univariate sensitivity analyses highlight the principal sources of uncertainty in quantifying population survival gains attributable to ART during 2004–2011. However, because survival gains are calculated as the difference in survival between a cohort receiving ART and an identical cohort not receiving ART, sensitivity analyses of parameters informing population characteristics (eg, CD4<sup>+</sup> T-cell count) are not comparisons of alternative ART initiation policies. Instead, these results represent a measure of the impact on survival gain estimates of the uncertainty in the mean CD4<sup>+</sup> T-cell counts of all HIV-infected patients initiating ART in South Africa during 2004–2011. Indeed, while cohort data from sub-Saharan Africa demonstrate that ART initiation at higher CD4<sup>+</sup> T-cell counts results in increased survival [43], our results demonstrate the relative insensitivity of survival gains to the cohort mean CD4<sup>+</sup> T-cell count. The limited impact of CD4<sup>+</sup> T-cell count at ART initiation reflects a counterbalancing of increased survival in the treatment scenario by increased survival in the counterfactual scenario without ART.

The results of this study reflect an intentionally conservative estimate of survival benefits attributable to ART in South Africa. The base-case scenario assumed that no additional persons enrolled in ART beyond those already being treated as of the end of 2010, that no improvement in ART efficacy

occurred, and that second-line ART availability was limited to 2.4% of all persons being treated with ART. The analyses of more-frequent testing and more-comprehensive treatment policies demonstrate dramatic increases in survival benefits when these unfavorable assumptions are relaxed, with the potential to more than double the survival benefits under current policies by 2030 in the most-expanded linkage to care and treatment scenarios.

Our analysis demonstrates substantial survival benefits in a scenario of future increased linkage to care of untreated HIV-infected persons eligible for ART but not yet receiving treatment [44]. Indeed, the UNAIDS estimates that one-third of HIV-infected persons living in South Africa who are eligible for ART are not yet receiving treatment [1], posing an opportunity to expand access to life-extending medication [11, 45]. Such expansion will require 2 components. First, expanded case detection through HIV testing will be necessary; national surveys suggest that half of South Africans have never been tested for HIV [46]. Second, as case detection increases, larger numbers of HIV-infected persons will be identified before they are eligible for ART, and so it will become increasingly important to track and monitor these persons until they are eligible for ART. Furthermore, our sensitivity analyses illustrate that the rate at which untreated eligible patients are linked to care drives survival benefits, demonstrating the impact of speed of scale-up on survival [13]. Base-case survival benefits as of 2030 range from 17.9 million life-years without linkage to care of any additional patients to 29.4 million life-years with immediate linkage to care of 84% of untreated patients eligible for ART each year.

This analysis has several limitations. First, the total survival benefit estimates relied on the accuracy of UNAIDS data on the numbers of persons receiving ART each year [1]. Second, the model does not capture the benefits of preventing secondary transmission. Third, our analysis considers only adults, neglecting survival benefits attributable to prevention of mother-to-child transmission [47] and treatment of HIV-infected children [48]. Finally, our future survival gain projections to 2030 and beyond rely on many assumptions, including predictable epidemic growth, stable health and demographic characteristics of ART recipients, consistent HIV treatment policy and ART program performance, reliable treatment-funding sources, and stable treatment efficacy. To the extent that any of these assumptions do not reflect reality, our projections regarding the future benefit of ART and ART policy changes would differ accordingly.

Since emerging as the epicenter of the HIV pandemic in the early 1980s, South Africa has endured devastating losses, with AIDS-related deaths exceeding 200 000 persons each year since 2001 [1]. These deaths have undermined families, societies, and economies throughout the country. This analysis highlights the dramatic capacity for HIV treatment to stem this tide of disease in South Africa, projecting 2.8 million years of life already gained. That said, this analysis finds that the lifetime survival



benefits attributable to ART in South Africa by 2030 range from 17.9 million life-years under current treatment policies up to 35.6 million with a combination of aggressive linkage to care and unrestricted second-line ART availability. Realization of these future potential benefits will require not only drugs but also commitment by the international community to continue implementing and refining effective treatment programs and practices.

## Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online (<http://jid.oxfordjournals.org/>). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

## Notes

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Dr April had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs April, Walensky, Wood, and Anglaret were involved in the study concept and design. Drs April, Wood, Anglaret, and Berkowitz were involved in data acquisition. Drs April, Walensky, Berkowitz, Wood, Paltiel, Losina, Freedberg, and Anglaret were involved in the analysis and interpretation of data. Dr April was involved in manuscript drafting. Drs April, Walensky, Wood, Berkowitz, Paltiel, Losina, Freedberg, and Anglaret were involved in manuscript revision. Drs April, Losina, Berkowitz, Walensky, and Paltiel were involved in statistical analysis. Drs Walensky, Paltiel, Freedberg, Losina, Wood, and Anglaret were involved in obtaining funding. Drs April and Berkowitz were involved in providing administrative, technical, or material support. Drs April, Walensky, Paltiel, and Losina were involved in study supervision.

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

## References

1. Joint United Nations Programme on HIV/AIDS. AIDSinfo database. Geneva: Joint United Nations Programme on HIV/AIDS, 2012. <http://www.unaids.org/en/dataanalysis/tools/aidsinfo/>. Accessed 4 August 2013.
2. National Department of Health South Africa. National antiretroviral treatment guidelines. Pretoria: Jacana, 2004. <http://southafrica.usembassy.gov/media/2004-doh-art-guidelines.pdf>. Accessed 4 August 2013.
3. National Department of Health South Africa. The South African antiretroviral treatment guidelines. Pretoria: South African National AIDS Council, 2010. [http://sonkepharmaceuticals.co.za/images/stories/documents/the\\_south\\_african\\_antiretroviral\\_treatment\\_guidelines.pdf](http://sonkepharmaceuticals.co.za/images/stories/documents/the_south_african_antiretroviral_treatment_guidelines.pdf). Accessed 4 August 2013.
4. United Nations General Assembly. Political declaration on HIV and AIDS: intensifying our efforts to eliminate HIV and AIDS. New York, NY: United Nations General Assembly, 2011. [http://www.unaids.org/en/media/unaids/contentassets/documents/document/2011/06/20110610\\_un\\_a-res-65-277\\_en.pdf](http://www.unaids.org/en/media/unaids/contentassets/documents/document/2011/06/20110610_un_a-res-65-277_en.pdf). Accessed 4 August 2013.
5. National Department of Health. Operational plan for comprehensive HIV and AIDS care, management and treatment for South Africa. Pretoria: National Department of Health, 2003. <http://www.info.gov.za/otherdocs/2003/aidsplan/index.html>. Accessed 4 August 2013.
6. Joint United Nations Programme on HIV/AIDS. Global report: UNAIDS report on the global AIDS epidemic. Geneva: Joint United Nations Programme on HIV/AIDS, 2012. [http://www.unaids.org/en/media/unaids/contentassets/documents/epidemiology/2012/gr2012/20121120\\_UNAIDS\\_Global\\_Report\\_2012\\_en.pdf](http://www.unaids.org/en/media/unaids/contentassets/documents/epidemiology/2012/gr2012/20121120_UNAIDS_Global_Report_2012_en.pdf). Accessed 4 August 2013.
7. Cohen RL, Li Y, Giese R, Mancuso JD. An evaluation of the President's Emergency Plan for AIDS Relief effect on health systems strengthening in sub-Saharan Africa. *J Acquir Immune Defic Syndr* 2013; 62:471–9.
8. Bendavid E, Holmes CB, Bhattacharya J, Miller G. HIV development assistance and adult mortality in Africa. *JAMA* 2012; 307:2060–7.
9. Bor J, Herbst AJ, Newell ML, Barnighausen T. Increases in adult life expectancy in rural South Africa: valuing the scale-up of HIV treatment. *Science* 2013; 339:961–5.
10. Walensky RP, Paltiel AD, Losina E, et al. The survival benefits of AIDS treatment in the United States. *J Infect Dis* 2006; 194:11–9.
11. Walensky RP, Wood R, Fofana MO, et al. The clinical impact and cost-effectiveness of routine, voluntary HIV screening in South Africa. *J Acquir Immune Defic Syndr* 2011; 56:26–35.
12. Goldie SJ, Yazdanpanah Y, Losina E, et al. Cost-effectiveness of HIV treatment in resource-poor settings—the case of Côte d'Ivoire. *N Engl J Med* 2006; 355:1141–53.
13. Walensky RP, Wood R, Weinstein MC, et al. Scaling up antiretroviral therapy in South Africa: the impact of speed on survival. *J Infect Dis* 2008; 197:1324–32.
14. Rosen S, Fox MP, Gill CJ. Patient retention in antiretroviral therapy programs in sub-Saharan Africa: a systematic review. *PLoS Med* 2007; 4:e298.
15. Fox MP, Rosen S. Patient retention in antiretroviral therapy programs up to three years on treatment in sub-Saharan Africa, 2007–2009: systematic review. *Trop Med Int Health* 2010; 15(Suppl 1):1–15.
16. Mellors JW, Muñoz A, Giorgi JV, et al. Plasma viral load and CD4+ lymphocytes as prognostic markers of HIV-1 infection. *Ann Intern Med* 1997; 126:946–54.
17. Holmes CB, Wood R, Badri M, et al. CD4 decline and incidence of opportunistic infections in Cape Town, South Africa: implications for prophylaxis and treatment. *J Acquir Immune Defic Syndr* 2006; 42:464–9.
18. United Nations Department of Economic and Social Affairs Population Division. World population prospects: the 2008 revision. New York: United Nations, 2009. [http://www.un.org/esa/population/publications/wpp2008/wpp2008\\_highlights.pdf](http://www.un.org/esa/population/publications/wpp2008/wpp2008_highlights.pdf). Accessed 4 August 2013.
19. Yazdanpanah Y, Losina E, Anglaret X, et al. Clinical impact and cost-effectiveness of co-trimoxazole prophylaxis in patients with HIV/AIDS in Côte d'Ivoire: a trial-based analysis. *AIDS* 2005; 19:1299–308.
20. World Health Organization. Antiretroviral therapy for HIV infection in adults and adolescents. Geneva: World Health Organization, 2006. <http://www.who.int/hiv/pub/guidelines/artadultguidelines.pdf>. Accessed 4 August 2013.
21. World Health Organization. Progress report 2011: global HIV/AIDS response. Geneva: World Health Organization, 2011. [http://www.who.int/hiv/pub/progress\\_report2011/en/index.html](http://www.who.int/hiv/pub/progress_report2011/en/index.html). Accessed 4 August 2013.
22. Ahonkhah AA, Noubary F, Munro A, et al. Not all are lost: interrupted laboratory monitoring, early death, and loss to follow-up (LTFU) in a large South African treatment program. *PLoS One* 2012; 7:e32993.

23. Morrow C, Munro A, Wilke M, Stark R, Wood R. Remote sensing of HIV care programmes using centrally collected laboratory results: can we monitor ART programme effectiveness?. *S Afr Med J* **2012**; 102:501–5.
24. Losina E, Yazdanpanah Y, Deuffic-Burban S, et al. The independent effect of highly active antiretroviral therapy on severe opportunistic disease incidence and mortality in HIV-infected adults in Côte d'Ivoire. *Antivir Ther* **2007**; 12:543–51.
25. Barth RE, van der Loeff MF, Schuurman R, Hoepelman AI, Wensing AM. Virological follow-up of adult patients in antiretroviral treatment programmes in sub-Saharan Africa: a systematic review. *Lancet Infect Dis* **2010**; 10:155–66.
26. Tuboi SH, Brinkhof MW, Egger M, et al. Discordant responses to potent antiretroviral treatment in previously naive HIV-1-infected adults initiating treatment in resource-constrained countries: the antiretroviral therapy in low-income countries (ART-LINC) collaboration. *J Acquir Immune Defic Syndr* **2007**; 45:52–9.
27. World Health Organization. Towards universal access. Geneva: World Health Organization, **2010**. [http://whqlibdoc.who.int/publications/2010/9789241500395\\_eng.pdf](http://whqlibdoc.who.int/publications/2010/9789241500395_eng.pdf). Accessed 4 August 2013.
28. Brinkhof MW, Pujades-Rodriguez M, Egger M. Mortality of patients lost to follow-up in antiretroviral treatment programmes in resource-limited settings: systematic review and meta-analysis. *PLoS One* **2009**; 4:e5790.
29. Van Cutsem G, Ford N, Hildebrand K, et al. Correcting for mortality among patients lost to follow up on antiretroviral therapy in South Africa: a cohort analysis. *PLoS One* **2011**; 6:e14684.
30. Nglazi MD, Lawn SD, Kaplan R, et al. Changes in programmatic outcomes during 7 years of scale-up at a community-based antiretroviral treatment service in South Africa. *J Acquir Immune Defic Syndr* **2011**; 56:e1–8.
31. World Health Organization. Scaling up antiretroviral therapy in resource-limited settings. Geneva: WHO, **2002**. [http://www.who.int/hiv/pub/prev\\_care/en/ScalingUp\\_E.pdf](http://www.who.int/hiv/pub/prev_care/en/ScalingUp_E.pdf). Accessed 4 August 2013.
32. World Health Organization. Antiretroviral therapy for HIV infection in adults and adolescents. Geneva: World Health Organization, **2010**.
33. Coetzee D, Hildebrand K, Boule A, et al. Outcomes after two years of providing antiretroviral treatment in Khayelitsha, South Africa. *AIDS* **2004**; 18:887–95.
34. Seyler C, Anglaret X, Dakoury-Dogbo N, et al. Medium-term survival, morbidity and immunovirological evolution in HIV-infected adults receiving antiretroviral therapy, Abidjan, Côte d'Ivoire. *Antivir Ther* **2003**; 8:385–93.
35. Hammond R, Harry TC. Efficacy of antiretroviral therapy in Africa: effect on immunological and virological outcome measures—a meta-analysis. *Int J STD AIDS* **2008**; 19:291–6.
36. Gallant JE, DeJesus E, Arribas JR, et al. Tenofovir DF, emtricitabine, and efavirenz vs. zidovudine, lamivudine, and efavirenz for HIV. *N Engl J Med* **2006**; 354:251–60.
37. Johnson M, Grinsztejn B, Rodriguez C, et al. Atazanavir plus ritonavir or saquinavir, and lopinavir/ritonavir in patients experiencing multiple virological failures. *AIDS* **2005**; 19:685–94.
38. Actuarial Society of South Africa. ASSA2008 model. Cape Town, South Africa: Actuarial Society of South Africa, **2011**. <http://aids.actuarialsociety.org.za/Models-3145.htm>. Accessed 4 August 2013.
39. Lawn SD, Myer L, Harling G, et al. Determinants of mortality and non-death losses from an antiretroviral treatment service in South Africa: implications for program evaluation. *Clin Infect Dis* **2006**; 43:770–6.
40. Stover J, Korenromp EL, Blakley M, et al. Long-term costs and health impact of continued global fund support for antiretroviral therapy. *PLoS One* **2011**; 6:e21048.
41. Resch S, Korenromp E, Stover J, et al. Economic returns to investment in AIDS treatment in low and middle income countries. *PLoS One* **2011**; 6:e25310.
42. Joint United Nations Programme on HIV/AIDS. What countries need—investments needed for 2010 targets. Geneva: Joint United Nations Programme on HIV/AIDS, **2009**. [http://data.unaids.org/pub/Report/2009/jc1681\\_what\\_countries\\_need\\_en.pdf](http://data.unaids.org/pub/Report/2009/jc1681_what_countries_need_en.pdf). Accessed 4 August 2013.
43. Sterne JA, May M, Costagliola D, et al. Timing of initiation of antiretroviral therapy in AIDS-free HIV-1-infected patients: a collaborative analysis of 18 HIV cohort studies. *Lancet* **2009**; 373:1352–63.
44. Rosen S, Fox MP. Retention in HIV care between testing and treatment in sub-Saharan Africa: a systematic review. *PLoS Med* **2011**; 8:e1001056.
45. April MD. Rethinking HIV exceptionalism: the ethics of opt-out HIV testing in sub-Saharan Africa. *Bull World Health Organ* **2010**; 88:703–8.
46. Shisana O, Rehle T, Simbayi L, et al. South African National HIV Prevalence, Incidence, Behaviour and Communication Survey, 2008. Cape Town: HSRC Press, **2009**. <http://www.mrc.ac.za/pressreleases/2009/sanat.pdf>. Accessed 4 August 2013.
47. Ciaranello AL, Perez F, Engelsmann B, et al. Cost-effectiveness of World Health Organization 2010 guidelines for prevention of mother-to-child HIV transmission in Zimbabwe. *Clin Infect Dis* **2013**; 56: 430–46.
48. Meyer-Rath G, Brennan A, Long L, et al. Cost and outcomes of paediatric antiretroviral treatment in South Africa. *AIDS* **2013**; 27:243–50.